RESEARCH ARTICLE

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Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial†

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Background: Depression is common in nursing home (NH) patients with dementia, and often clustered with anxiety and other mood symptoms. An association between pain and depressive symptoms has been reported, but the impact of pain management on depression and other mood symptoms has not been investigated.

Objective: Secondary analyses of a cluster randomized clinical trial examine the response of dementia-related mood symptoms to a Stepwise Protocol of Treating Pain.

Method: Three-hundred fifty-two patients with moderate and severe dementia and significant behavioural disturbances, related to 60 clusters (i.e. clusters defined as single independent NH units) in 18 NHs of Western Norway, were included. All patients in the intervention group received individual daily pain treatment with paracetamol, extended release morphine, buprenorphine transdermal patch or pregabaline for 8 weeks, with additional follow-up assessment 4 weeks after completion of the intervention. Clusters randomized to control received usual treatment. A mood cluster consisting of depression, anxiety, sleep disorders, apathy and appetite items from the Neuropsychiatric Inventory-Nursing Home (NPI-NH) was the primary outcome.

Results: Analysed by Mann–Whitney *U*-tests, Stepwise Protocol of Treating Pain conferred significant benefit in treatment of the NPI-NH mood cluster ($F = 13.4$, $df = 1;299$, $p < 0.001$) and depression ($F = 2.0$, $df = 1;301$, $p = 0.025$). Further analyses highlighted improvements in apathy ($F = 5.3$, $df = 1;300$, $p = 0.017$), night-time behaviours ($F = 3.1$, $df = 1;301$, $p = 0.050$), and appetite items ($F = 11.6$, $df = 1;301$, $p = 0.005$), but not irritability ($p = 0.092$) and anxiety ($p = 0.125$).

Conclusion: Mood symptoms including depression significantly improved with pain treatment, emphasizing the importance of more rigorous treatment of pain in agitated people with dementia. Findings have potentially immediate clinical relevance. © 2013 The Authors. *International Journal of Geriatric Psychiatry* published by John Wiley & Sons Ltd.

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Introduction

In nursing homes (NH), 80% of the patients have dementia, and of them, 90% have one or more neuropsychiatric symptoms (NPSs) (Selbaek *et al.*, 2008). The most frequently occurring of the NPS are depression, apathy and anxiety (Robert *et al.*, 2005). The prevalence of these symptoms differs in accordance to the diagnoses and severity of dementia. In patients with Alzheimer's disease, about 50% will have

depressive symptoms at some stage of the disease (Lyketsos and Olin, 2002). In vascular dementia, depression is expected at least as common as in Alzheimer's dementia (Ballard *et al.*, 2000). In Norwegian NHs, depressive symptoms occur in about 21% of all patients, with follow-up incidence of 14.9% and persistence rate 44.8% after 1 year (Selbaek *et al.*, 2008).

Although depressive symptoms might fluctuate over time, depression hastens cognitive decline (Rapp *et al.*, 2011), has a negative impact on the quality of life (St John and Montgomery, 2010) and worsens functional impairment (Starkstein *et al.*, 2005). Other mood disorders such as apathy, anxiety, nigh-time behaviours and appetite and eating disorders are less well studied but also frequent and impactful in these individuals (Aalten *et al.*, 2003; Hollingworth *et al.*, 2006; Wetzels *et al.*, 2010). Thus, the five-year prevalence of apathy and anxiety is about 70 and 60%, respectively (Steinberg *et al.*, 2008), whereas nigh-time behaviours, and appetite and eating disorders increase to over 40% in patients with severe dementia (Craig *et al.*, 2005).

As in non-demented populations, depressed mood is usually accompanied by other related symptoms. This is also reflected in the proposed diagnostic criteria for depression in Alzheimer's disease, which in addition to the core symptoms depressed mood and anhedonia, also includes symptoms such as disturbance of sleep and appetite (Olin *et al.*, 2002). Similarly, several studies have found that NPSs tend to cluster into broader syndromes such as agitation, psychosis and mood syndromes (Aalten *et al.*, 2003; Hollingworth *et al.*, 2006; Wetzels *et al.*, 2010; Cheng *et al.*, 2012; Selbaek and Engedal, 2012). Additionally, a prevalence study focussing on patients in psychogeriatric wards of Dutch NHs reported that irritability was one of the most prominent features of depression in people with dementia (Verkaik *et al.*, 2009).

Antidepressants have been the usual treatment for patients with depressive symptoms and dementia. However, systematic reviews and meta-analyses could not find benefit of the treatment (Bains *et al.*, 2002; Thompson *et al.*, 2007; Nelson and Devanand, 2011). Two most recent and larger trials of antidepressants did not confirm the efficacy of antidepressants compared with placebo but increased the risk of adverse events in the intervention group in depressed people with dementia (Weintraub *et al.*, 2010; Banerjee *et al.*, 2011). Another large-scale study found that selective serotonin reuptake inhibitors were associated with significant higher rates of all-cause mortality, stroke, falls or fractures (Coupland *et al.*, 2011). Despite these results, antidepressants are frequently used in NH residents with dementia (Ruths *et al.*, 2012). Thus, there is an urgent need for new and improved treatment strategies to contribute to the management of depressive symptoms in people with dementia.

The aetiology of depressive symptoms in dementia is largely unknown. However, in addition to brain changes such as white-matter lesions, unmet psychological needs such as pain may be associated with increased NPSs in patients with dementia (Ballard *et al.*, 2009). Although few studies have explored such relationship (Ballard *et al.*, 1996), it was suggested that patients with moderate dementia and pain express the highest levels of depression (Cohen-Mansfield and Taylor, 1998), and that moderate dementia exacerbate the impact of pain on depression in NH patients and elderly people living at home (Walid and Zaytseva, 2009). Therefore, it is a key question whether pain treatment could improve depression and other mood symptoms in patients with advanced dementia.

The purpose of this study was to examine the effect of a Stepwise Protocol of Treating Pain (SPTP) on the two primary outcome measures of the composite mood syndrome scores and the depression item assessed by the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) (Cohen-Mansfield and Libin, 2004). Secondary outcome measures were the other items included in the mood syndrome, that is, apathy, anxiety, night-time behaviours and appetite and eating disorders. In addition, the effect of the SPTP on irritability was investigated.

Methods

Subjects

Nine-hundred-forty patients of 18 NHs on the West coast of Norway were screened for participation in the study. The original pool of participants consisted of 420 patients with moderate and severe dementia and significant behavioural disturbances. Data collection was performed October 2009 to June 2010. The recruitment strategy, patient samples and design of this study have also been described elsewhere (Husebo *et al.*, 2011). In brief, eligible participants were adults ≥65 years, living in the NH for at least 4 weeks, with moderate or severe dementia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Functional Assessment Staging score >4 (Reisberg, 1988), and clinical relevant behavioural disturbances defined as Cohen-Mansfield Agitation Inventory score ≥39 (Cohen-Mansfield and Libin, 2004). Exclusion criteria were advanced medical disease with expected

survival ≤6 months, severe psychiatric or neurological disorders (NPI-NH agitation score ≥8, with aggression as predominant symptom) (Selbaek *et al*., 2007), and allergy to paracetamol, extended release morphine, buprenorphine or pregabaline. The final sample included 352 participants (Husebo *et al*., 2011).

Ethics

Written informed consent included a description of the study design, direct benefit and possible side effects of the trial. Because individuals with mild cognitive impairment have an impaired capacity to consent to research (Ayalon, 2009), informed consent was obtained from all patients, and all surrogates/caregivers or the authorized legal representative. In accordance with local law, the study was approved by the Regional Committee for Medical Ethics, Western Norway (REK-Vest 248.08) and by the authorized Institutional Review Board of each participating institution. Caregivers also give consent to participate as informants.

Study design

This was a cluster randomized controlled trial for 8 weeks (treatment period) with an additional follow-up 4 weeks after the end of treatment at 12 weeks (wash-out period) to see whether symptoms reappeared after treatment withdrawal. A cluster was defined as single independent NH unit. Thus, patients related to the clusters were randomly assigned to receive SPTP in the intervention group or continued with their usual management (control group). A computer-generated list of random numbers was used for allocation of the clusters by the study statistician using Stata version 8 (StataCorp LP). Patients were examined at baseline and 2, 4 and 8 week, as well as at the end of the wash-out period at week 12. The treating physicians were instructed to keep prescriptions and doses of psychotropic medications unchanged, and none of the patients started with antidepressants during the 8-week period.

Procedure

The research group, consisted of an anaesthetist and pain therapist (B. S. H), a research assistant (R. K. S.), the responsible NH physician and the patient's primary caregiver, investigated each single patient. Together with the patients' primary care givers, two trained research assistants retrieved data pertaining to background variables, which included information about sex, age, medical information (diagnoses, and pain diagnoses) and list of medication taken. Attempts were made to keep the patients, the primary care givers and the research assistants blinded about the study design and type of intervention.

Outcome measures

The NPI-NH is a 12-item instrument to assist caregivers to rate the frequency and severity with which NH patients manifest NPSs (Selbaek *et al*., 2007). The rating was made by a trained research assistant based on a face-to-face interview with the caregiver who was familiar with the patient.

Neuropsychiatric Inventory-Nursing Home items are rated on a 1 to 4 point scale of frequency, ranging from (1) Occasionally—less than once per week; (2) Often—about once per week; (3) Frequently—several times a week but less than every day; (4) Very frequently—daily or essentially continuously present. The severity is rated as (1) Mild—produce little distress in the patient; (2) Moderate—more disturbing to the patient but can be redirected by the caregiver; (3) Severe—very disturbing to the patient and difficult to redirect. For each item a composite score is calculated as frequency (F) × severity (S), with a maximum score = 12. Dependent items are present or absent by a cut-off $F \times S <$ or ≥ 4. Good validity and reliability of the Norwegian version of the NPI-NH has been reported (Selbaek *et al*., 2007).

The two primary outcome measures in the current study were the depression item and the composite mood syndrome scores. Secondary outcome measures were the other items included in the mood syndrome, that is, apathy, anxiety, night-time behaviours and appetite and eating disorders (Olin *et al*., 2002; Cheng *et al*., 2012). The effect of treating pain on irritability was also determined as a further exploratory analysis (Verkaik *et al*., 2009).

Pain was assessed by the Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale, a staff-administered observational pain behaviour assessment instrument, developed and tested in NH patients with advanced dementia (Husebo *et al*., 2010).

Intervention

The SPTP was based on the recommendations of the American Geriatrics Society (AGS Panel, 2009). Depending on the on-going medical treatment, participants received paracetamol oral (max. increase to 3 g/day), extended release morphine oral (max.

20 mg/day), and/or pregabaline oral (max. 300 mg/d) using a fixed dose regime. Patients with swallowing difficulties were treated with buprenorphine transdermal patch (max. 10 µg/h/7 days). Medication was offered at breakfast, lunch and dinner (approximately 8:00 AM, noon, 6:00 PM), respectively. If needed, it was allowed to combine different medications. In patients who were not able to tolerate this treatment, the dosage was reduced or the patient was withdrawn from study and treated as clinically appropriate.

Statistical analysis

Demographic and clinical characteristics between the control and intervention group at baseline were compared using chi-square for categorical variables, Independent-Samples *T*-test for normal and Mann–Whitney *U*-test for non-normal distributed continuous variables. In addition, Mann–Whitney *U*-test was used to investigate the influence of pain treatment on the composite mood syndrome scores (depression, apathy, anxiety, night-time behaviours and appetite

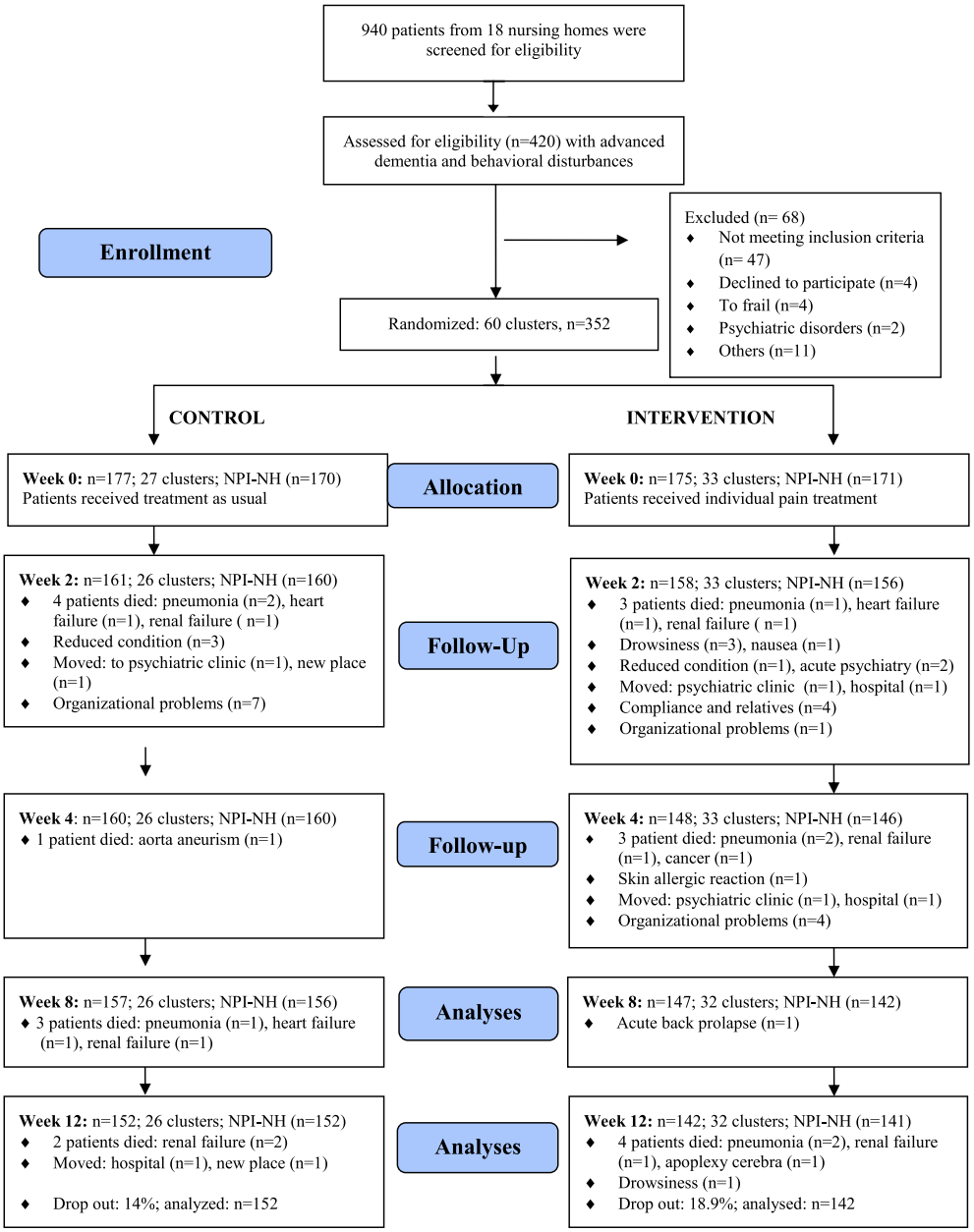

Figure 1 Study flow diagram.

and eating disorders), and to address whether the change in depressive symptoms at week 8 is associated with the use of antidepressants. Additionally, the analgesic effect on irritability was investigated. To explore whether the improvement in mood syndrome and the other items were associated with reduced pain, we correlated the change scores in these items with change scores in pain using Spearman rho correlation.

Treatment effect was expressed as estimated effect of intervention, along with a 95% confidence interval and the *p*-values for each time point. *p*-values less than 0.05 were considered as statistically significant. Standardized effect sizes (ES) were calculated as mean change divided by the baseline standard deviation (SD). For clinical relevance, the size of ES is conventionally classified as being large (0.5), moderate (0.3) or small (0.1) (Field, 2005). Statistical analyses were performed using the software program SPSS 13.0 (SPSS, Inc., Chicago, IL).

Results

Three-hundred fifty-two patients in 60 clusters were finally randomized (177 patients in the control and 175 in pain treatment group) (Figure 1); 170 patients in the control and 171 in the intervention group were assessed by NPI-NH at baseline. Demographic and clinical characteristics at baseline are shown in Table 1. The intervention group was slightly younger and with a smaller proportion on

Table 1 Background characteristics of patients at baseline for the control and intervention group

	Control ($n = 177$)	Intervention ($n = 175$)	Statistics	
			df	*p*
Age[a]	86.5 (6.7)	84.9 (7.0)	1;350	0.022
Female[b]	131 (74.0)	131 (74.9)	1	0.856
MMSE[a]	8.4 (6.7)	7.5 (6.4)	1:346	0.209
NPI-NH total score[c]	31.4 (21.4)	34.8 (21.9)	1;339	0.143
NPI-NH[c]—mood cluster	16.3 (12.5)	18.3 (13.0)	1;340	0.291
NPI-NH[c]—depression	2.8 (3.6)	2.8 (3.5)	1;341	0.902
NPI-NH[c]—apathy	2.5 (3.6)	3.5 (4.2)	1;341	0.041
NPI-NH[c]—anxiety	3.1 (4.0)	3.4 (4.2)	1;341	0.481
NPI-NH[c]—irritability	3.7 (3.7)	4.2 (4.1)	1;341	0.338
NPI-NH[c]—sleep	2.2 (3.2)	1.9 (3.2)	1;341	0.295
NPI-NH[c]—appetite	2.5 (4.0)	2.5 (4.1)	1;341	0.884
Antidepressants[b]	94 (56.2)	74 (42.5)	1;341	0.013
Antipsychotics[b]	91 (54.5)	86 (49.4)	1;341	0.386

Numbers represent mean (SD) or number of patients (%).
MMSE, Mini-mental status examination; NPI-NH, Neuropsychiatric Inventory-Nursing Home version.
[a]Independent-Samples *T*-test.
[b]Pearson Chi-square (test statistics).
[c]Mann-Whitney *U*-test.

Table 2 Efficacy of pain treatment for single Neuropsychiatric Inventory-Nursing Home version item scores, the mood syndrome factor group and irritability, mean (SD) at baseline and week 8 for the control and intervention groups

	Baseline			Week 8		
	Control ($n = 170$)	Intervention ($n = 171$)	*p*-value[a]	Control ($n = 156$)	Intervention ($n = 142$)	*p*-value[a]
NPI-NH total score	31.9 (21.9)	33.8 (21.7)	0.132	26.6 (20.1)	18.9 (17.6)	<0.001
Mood symptom factor group	16.9 (12.5)	18.3 (13.0)	0.291	14.7 (11.5)	9.9 (10.6)	<0.001
Depression	2.9 (3.7)	2.5 (3.3)	0.902	2.1 (2.9)	1.6 (2.9)	0.025
Anxiety	3.2 (4.1)	3.3 (4.2)	0.481	2.5 (3.7)	1.8 (3.1)	0.125
Apathy	2.5 (3.6)	3.6 (4.3)	0.041	2.6 (3.7)	1.7 (3.3)	0.017
Irritability	3.7 (3.7)	4.2.(4.1)	0.388	2.9 (3.4)	2.3 (3.0)	0.092
Night-time behaviours	2.2 (3.3)	1.6 (2.7)	0.295	1.9 (3.1)	1.3 (2.6)	0.050
Appetite and eating disorders	2.5 (4.0)	2.4 (4.1)	0.884	2.7 (4.0)	1.3 (2.9)	0.005

NPI-NH, Neuropsychiatric Inventory-Nursing Home version.
[a]Analyzing the factor group scores for the control versus the intervention group from baseline to week 8 using Mann-Whitney *U*-test.

antidepressants than the control group, but the two groups did not differ in depression scores at baseline. During the 8 weeks, 20 and 28 patients were lost in the control and intervention group, respectively ($p = 0.298$) (Husebo *et al.*, 2011). There were 14 deaths during the study period, eight in the control and six in the intervention group.

High prevalence rates were shown for depression (34%), anxiety (38%), apathy (37%), irritability (32%), sleeping and night-time behaviours (25%), and appetite and eating disturbances (28%). Table 2 and Figure 2 show the change on the composite mood syndrome scores, depression and the other items. The depression and composite mood scores declined in both groups. However, the changes of both the primary outcome measures differed significantly between the two groups in favour of pain treatment: composite mood syndrome ($F = 13.4$, $df = 1;299$, $p < 0.001$, ES = 0.6), and depression item ($F = 2.0$, $df = 1;301$, $p = 0.025$, ES = 0.3). Changes over the treatment period (week 0–12) are shown in Figure 2. Similarly, significant differences were found for the

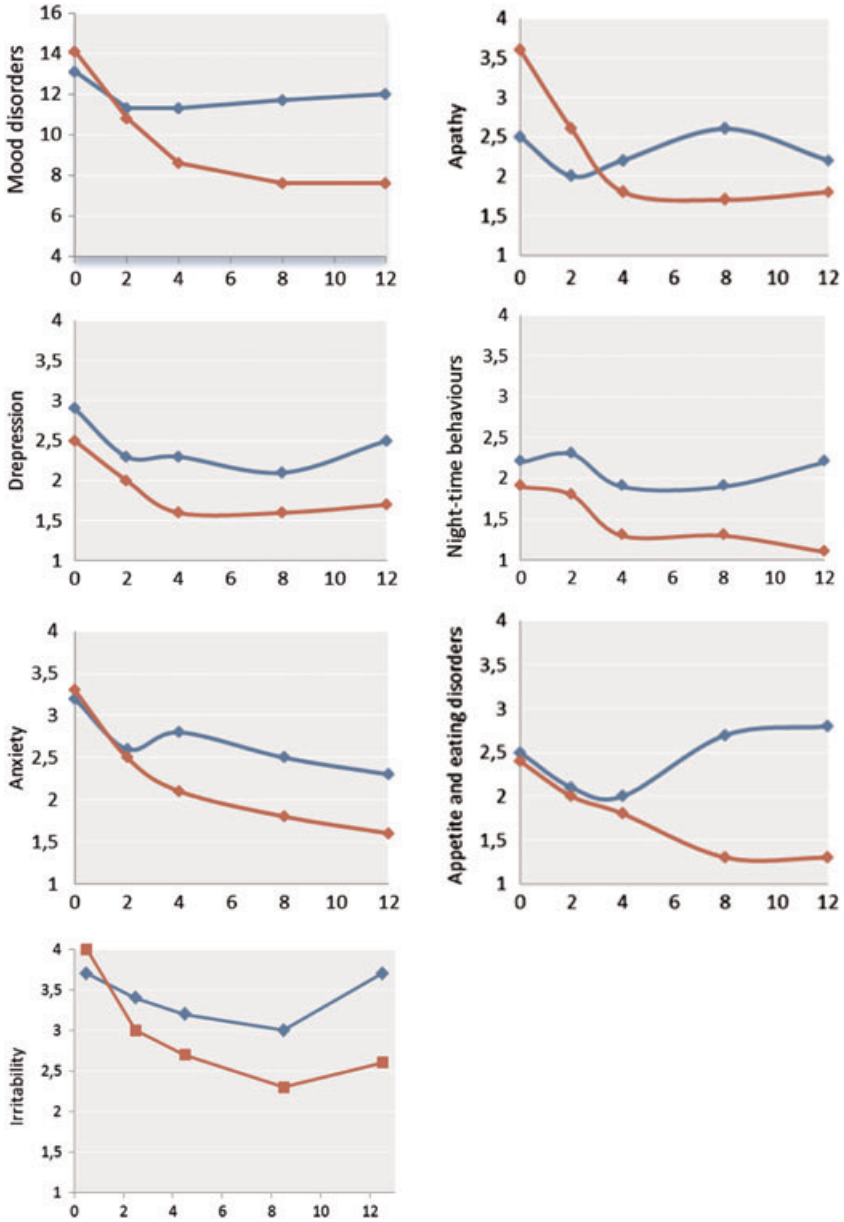

Figure 2 Change in the pain treatment and control groups in the mood syndrome factor group (depression, anxiety, apathy, irritability, night-time behaviours and appetite and eating disorders) and on single items of the Neuropsychiatric Inventory-Nursing Home version compared with control group and mean values at baseline, week 2, 4, 8 and 12.

secondary variables, apathy ($F = 5.3$, $df = 1;300$, $p = 0.017$, ES = 0.6), night-time behaviours ($F = 3.1$, $df = 1;301$, $p = 0.050$, ES = 0.1), and appetite and eating disorders ($F = 11.6$, $df = 1;301$, $p = 0.005$, ES = 0.4), whereas the difference on irritability ($F = 2.0$, $df = 1;301$, $p = 0.092$, ES = 0.3) and anxiety ($F = 3.0$, $df = 1;300$, $p = 0.125$, ES = 0.5) did not reach statistical significance.

After 8 weeks, change scores of the composite mood syndrome were found to be significantly correlated to change in pain (Spearman rho = 0.147, $p = 0.012$). In addition, the change scores of depression, apathy and irritability were correlated with change in pain (rho = 0.127, $p = 0.030$; rho = 0.154, $p = 0.008$; rho = 0.182, $p = 0.002$), respectively. The pain treatment effect on change scores of depression was independent ongoing antidepressant therapy ($p = 0.466$) in the intervention group at week 8.

Discussion

Analyses of an RCT study indicate that stepped pain treatment confers significant benefits on the composite mood syndrome in NH patients with dementia and agitation. Results support the idea that undiagnosed and untreated pain are important cofactors in the genesis of distressing mood symptoms such as depression, apathy, night-time behaviours and appetite and eating disorders. Reduction of pain in the treatment group after 8 weeks was correlated with change scores of the composite mood syndrome, depression, apathy and irritability findings support the hypothesis that the reduction of these symptoms was indeed secondarily related to reduced pain.

Analyses underline earlier assumptions that depressive symptoms in patients with dementia is at least partly caused by pain, and thus large-scale placebo-controlled studies to investigate the benefit of pain treatment on depression are warranted. Our results parallel research with younger age groups, in which there is a high occurrence of depression in chronic pain samples and even without organic basis for the pain (Casten *et al*., 1995). Moreover, depression is described to be strongly related to pain in individuals with cancer (Kirkova *et al*., 2010). Although these interactions of comorbidities are accepted in general, this link has surprisingly seldom been investigated in NH patients with dementia (Ballard *et al*., 1996).

Our study corroborates and extends prior research showing high apathy rates among patients with advanced dementia (Landes *et al*., 2001). At baseline, we found apathy directly correlated to reduced activities in daily living ($p < 0.001$) and to musculoskeletal pain assessed by MOBID-2 Pain Scale (part 1) (Husebo *et al*., 2010) ($p = 0.042$). Thus, findings of this study suggest that apathy may improve during pain treatment in patients with dementia. Although studies of apathy have been hampered by problems of definition, apathy is often described as a loss of motivation, interest and social engagement (Landes *et al*., 2001). Combined with pain, apathy seems to provoke a symptom spiral, which leads to the question whether pain increases apathy or apathy increases pain by inactivity and reduced mobilization. Family and staff may misinterpret apathetic patients as withdrawn, uninterested or insensitive (Casten *et al*., 1995). Thereby, evaluation of pain is a prerequisite to engage patients in rehabilitation, and physical and social activities.

In the current study, anxiety was significantly correlated to depression ($p < 0.001$), pain ($p = 0.016$), and sleeping and night-time behaviours ($p < 0.001$), at baseline. However, the change between the control and intervention groups did not differ during the 8 weeks. It might be speculated that increased attention and regular assessment and observation improved patients' anxiety and the overall judgement by staff. Although no treatment studies for anxiety in older adults or patients with dementia is available for direct comparison, data from cross sectional observational studies suggest an anxiety–pain interaction (Karp *et al*., 2008). In one study, anxiety was the only significant predictor of pain in a sample of patients over the age of 65 years receiving inpatient rehabilitation after orthopaedic surgery (Casten *et al*., 1995).

Although some researchers exclude night-time behaviours and appetite and eating disturbances from their analyses based on a 10-item NPI (Cheng *et al*., 2012), we investigated the pain treatment effect because these symptoms are frequent in NH patients with advanced dementia and may be closely related to pain and depression. In the current study, individuals with night-time behaviours were more in pain ($p = 0.032$), and used more antipsychotics ($p < 0.001$) and antidepressants ($p = 0.040$) compared with those without sleeping disorders.

Although not included in the suggested mood syndrome in dementia factor developed by Olin *et al*., (2002), more recent work has highlighted the importance of irritability as part of the depression in dementia syndrome (Verkaik *et al*., 2009), and the identified improvement in irritability with analgesic treatment is therefore notable.

In contrast to the results from another publication using the Cohen-Mansfield Agitation Inventory (Husebo *et al*., 2011), we could not find worsening of the mood symptoms during the 4-week wash-out phase. This is interesting and raises the question whether the NPI-NH is less sensible to assess changes in NPSs. A

more specific instrument such as the Cornell Scale for Depression in Dementia (Barca *et al.*, 2010) should be used in future research. Interestingly, change scores in mood were significantly but modestly correlated with change scores in pain. It is likely that the impact of analgesic treatment on mood is therefore multifactorial, and may include mechanisms not directly related to analgesia. As noted earlier, opioids may have an antidepressant effect in patients with affective disorders and refractory depression (Schaffer *et al.*, 2007). In one study, the antidepressant effect of the partial antagonist buprenorphine was noticed in patients with bipolar disorders (Bodkin *et al.*, 1995). However, no studies have investigated the affective response on analgesics in patients with advanced dementia.

Limitations

Several limitations of this study deserve comments, including the use of treatment as usual instead of placebo. We attempted to keep raters blind to the study objective and treatment, but double-blind, placebo-controlled studies of the effect of pain treatment on depression in dementia are required.

This article reports secondary analyses of a cluster randomized trial conducted for hypothesis generation purpose. Thereby, more detailed cluster variation (ICC) analyses to control for cluster effects have not been included. This should be acknowledged as an important consideration in the interpretation of the data.

Further, we used a composite mood syndrome following confirmatory factor analyses of a most recent study by Cheng *et al.*, 2012. However, factor groups may be viewed as merely theoretical constructs with uncertain clinical relevance and changes assessed over time (Selbaek and Engedal, 2012).

Analyses are based on primary inclusion criteria focusing on patients with agitation, and not on mood. Thus, we can only conclude that mood syndrome in people with advanced dementia and agitation seem to benefit from pain treatment, whereas future studies should test whether pain treatment can reduce depression in the dementia population.

In addition, the accuracy of proxy pain assessment may be impact by dementia-associated behavioural changes. For instance, high levels of depression may be associated with increased likelihood of pain rating because the patient's facial expression seems to be sad and worried. Thus, psychological symptoms like depression, anxiety and apathy, which also may be related to unmet needs such as grief, social isolation or soiled diaper may be misunderstood as pain (Corbett *et al.*, 2012).

Conclusion

This study investigated a simple question: has a stepwise protocol of treating pain directly impact on depressive symptoms in patients with dementia? We found that the composite mood syndrome, which includes NPSs like depression, apathy, irritability, night-time behaviours, and appetite and eating disorders responded to pain treatment in agitated persons with advanced dementia. Anxiety and irritability, however, did not benefit significantly by pain treatment. Mood symptoms are common and difficult to manage in dementia. It is crucial to follow up these results with a multicenter, parallel-group, double-blind RCT.

Conflict of interest

C. Ballard declares associations with the following companies: Acadia, Bristol-Myers Squibb, Esai, Janssen, Lundbeck, Novartis and Shire.

D. Aarsland declares associations with the following companies: DiaGenic, GE Healthcare, GlaxoSmithKline, Lundbeck, Merck Serono and Novartis. The other authors declare no competing interests.

Key points

- Untreated pain may be a co-factor for distressing mood symptoms in patients with advanced dementia.
- A stepwise protocol of pain treatment confers significant benefits in the composite mood syndrome scores and depression, apathy, night-time behaviours, and appetite and eating disorders, but not anxiety.
- Reduction of pain in the intervention group is correlated with change scores of the overall mood syndrome, depression, and apathy.

Ethics statement

This study was approved by the Regional Committee for Medical Research Ethics, Western Norway (REK-Vest nr: 248.08).

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Author contributions

B. S. H, C. B. and D. A. conceived the study and obtained funding. All authors contributed to the study design, carrying out the study, interpreted data and wrote the manuscript. B. S. H and R. S. collected data. B. S. H., F. F. and D. A. contributed to the statistical analysis. B. H. is the corresponding author.

Clinical study registration

The trial is registered at ClinicalTrials.gov, number NCT01021696 and at the Norwegian Medicines Agency (EudraCTnr: 2008-007490-20).

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